

Applicants: Jane H. Morse and James A. Knowles
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REMARKS

Claims 1-5, 7, 8, 10-19, 21-49, 51, 52 and 56 were pending in the subject application. Claim 56 was indicated as being allowable. By this Amendment, applicants have canceled claims 7, 8, 10-19 and 21-49 without disclaimer or prejudice. Claims 1-4 have been amended to make certain formatting changes. New claims 64 and 65 have been added. New claim 64 corresponds to canceled claims 10, 12, 14, 16, 18, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45 and 47. New claim 65 corresponds to canceled claims 11, 13, 15, 17, 19, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 48. No issue of new matter is raised by these amendments or by new claims 64 and 65. Accordingly, claims 1-5, 49, 51, 52, 64 and 65 will be pending and under examination in the subject application upon entry of this Amendment.

In view of the arguments below, applicants maintain that the ground of the Examiner's rejections have been overcome, and respectfully request that the rejections be withdrawn.

Rejection under 35 U.S.C. §112, First Paragraph

In the May 2, 2003 Office Action, the Examiner stated that claims 1-5, 7, 8, 49, 51, and 52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner stated that

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these claims encompass methods of detecting the broad genus of any possible mutation in the bone morphogenetic protein receptor-II (BMPRII) nucleic acid or protein, and correlating such a mutation with a pulmonary disease, giving birth to twins or triplets, or having a miscarriage. The Examiner further stated that the specification only provides a written description of the specific mutations as set forth in Figure 4, and claimed in claims 10-19, 21-48, and 56. The Examiner stated that the two relevant inquiries regarding this issue are: have a representative number of species been described by complete structure; and if not, have a representative number of species been described by sufficient relevant identifying characteristics. The Examiner then submitted that the answer is in the negative for both of these questions, and as such the genus claims cannot be justified. The Examiner also stated that while the specification discloses 19 gene-level mutations and their corresponding amino acid-level mutations, there is no description of any and every mutation which occurs in the BMPRII gene/protein, not to mention which ones correlate with a specific disease/condition and which are neutral polymorphisms. In summary, the Examiner stated that, at the time of the invention, the inventors were clearly not in possession of the subject matter embodied in the generic method claims.

In response, applicants respectfully traverse the Examiner's rejection.

The test for written description under 35 U.S.C. §112, first paragraph, is whether the disclosure describes the claimed invention in sufficient detail so that one skilled in the art

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can reasonably conclude that the inventor had possession of the claimed invention. According to M.P.E.P. §2163(I)(A), "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). The initial burden is therefore on the Examiner to present evidence of the lack of written description. Furthermore, according to M.P.E.P. §2163(II)(A)(3)(a), "[a]n adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. Applicants maintain that the claimed invention satisfies the test for adequate written description, and that the Examiner has not set forth sufficient grounds for concluding otherwise.

The subject invention provides methods of detecting whether a subject is either predisposed to or afflicted with pulmonary hypertension by detecting whether a mutation is present within the bone morphogenetic protein receptor-II (BPMR-II) gene. This invention is based on applicants' discovery of the role of mutations of the BPMR-II gene in pulmonary hypertension.

In support of the rejection, the Examiner alleges that a representative number of species have not been described by complete structure or by sufficient relevant identifying characteristics. The Examiner further alleges that there is no description of mutations which occur in the BPMR-II gene.

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Applicants disagree with the Examiner's position. As the Examiner concedes the specification discloses 19 gene-level mutations and their corresponding amino acid-level mutation. These mutations are identified in the instant specification, *inter alia*, at page 16, line 5 to page 23, line 17, summarized in Figure 4, by their location on the BPMR-II gene, i.e. exon number, their DNA sequence variation, i.e. deletion, insertion, or substitution of nucleic acids, and their corresponding protein sequence variation. In addition, Figure 2 schematically details the intron/exon structure of the BPMR-II gene and the corresponding mutations, both mutations that cause premature termination of BPMR-II and those found in Arg491. Applicants maintain that the disclosure of these relevant, identifying characteristics of the claimed invention is sufficient for a person skilled in the art to recognize that applicants were in possession of the claimed methods.

Moreover, according to M.P.E.P. §2163 (II)(A)(3)(a)(ii), the written description for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics sufficient to show the applicant was in possession of the claimed genus. *Regents of the University of California v Eli Lilly*, 119 F3d. 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). Satisfactory disclosure depends on whether the necessary common attributes of the genus are recognized by one skilled in the art in view of the species disclosed. It does not require that the description be so specific as to fully describe all species in the genus. Applicants maintain that the claimed genus is supported by the disclosed species, and that the species disclose the necessary attributes of the claimed genus.

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The claimed genus comprises mutations located on the BMPR-II gene which have been associated with the predisposition and onset of pulmonary hypertension. The disclosed species include 19 such mutations. Claim 1 provides a method of detecting a subject's predisposition to or affliction with pulmonary hypertension by detecting whether a mutation is present within the bone morphogenetic protein receptor-II (BPMR-II) gene. In assessing three potential gene candidates, CD28, CTLA4 and BPMR-II, applicants identified BMPR-II as the gene with mutations common to those afflicted with pulmonary hypertension. The location of these mutations on the BMPR-II gene is one of the common attributes of the claimed genus. One skilled in the pertinent art would recognize this attribute as a potential diagnostic tool. Accordingly, applicants maintain that one skilled in the art would easily recognize the commonality of the claimed genus in view of the disclosed species.

In view of these remarks, applicants maintain that claims 1-5, 51, 52 and new claims 64 and 65 are adequately supported by the disclosure and satisfy the requirements of 35 U.S.C. §112, first paragraph.

Claim Objection

The Examiner further stated that claim 56 is allowable, and that claims 10-19 and 21-48 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The Examiner stated that no prior art has been found teaching or suggesting

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detection of the specified mutations in the BMPR2 gene/protein and correlating them with the predisposition to/affliction of pulmonary disease, having twins or triplets, or having a miscarriage.

In response, applicants maintain that the amendments and arguments set forth hereinabove obviate the rejection under 35 U.S.C. §112, first paragraph, of claim 1-5, thereby providing proper dependency for new claims 64 and 65.

Summary

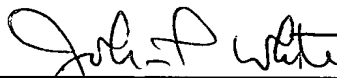
In view of the amendments and arguments set forth above, applicants maintain that the grounds of the Examiner's rejections and objections have been overcome. Applicants respectfully request that the Examiner reconsider and withdraw the rejections and objection, and solicit allowance of the claims now pending.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invite the Examiner to telephone him at the number provided below.

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No fee, other than the enclosed \$475.00 fee for the three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

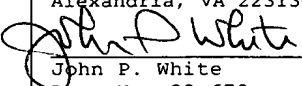
Respectfully submitted,



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